REMARKS/ARGUMENTS

Claims 1, 6, 7, 10, 11 and 108 were under examination. Claim 1 is amended. Claim 109 is new. No new matter has been added by the amendment.

Claim Amendments

Claim 1 is amended. Support for the element that "the naked anti-CEA MAb is unreactive with granulocytes" can be found at least at paragraphs [0048], [0049] and [0052] of the published Specification. Support for the element that "administration of the naked anti-CEA MAb to a cancer expressing CEA sensitizes the cancer to the subsequent administration of a cancer therapeutic agent" can be found at least at paragraphs [0107], [0293] and [0294] of the published Specification.

Claim 109 is new. Support can be found throughout the Specification at least at paragraphs [0003], [0008]-[0012], [0014], [0019], [0048], [0049], [0050], [0052], [0094]-[0096], [0098], [0103], [0104], [0107], [0109], [0114], [0249], [0250], [0287], [0288], [0293] and [0294].

Claim Rejections – 35 U.S.C. § 112, enablement

Claims 1, 6, 7, 10, 11 and 108 were rejected for "lacking of enablement for any combination therapy (any anti-CEA antibody with any apoptotic agent) producing a synergistic effect in treating human medullary thryroid carcinoma or human colorectal cancer." [Action at page 5.] Applicants respectfully traverse.

The action asserts, on page 5-6, that "Claim 1 encompasses any anti-CEA Mab (other than MN-14 of Claims 6 and 7), any apoptosis agent (other than those in Claims 10, 11 and 108), and any combination, which are not enabled by the specification . . ." Applicants submit that this assertion is fundamentally incorrect. First, Claim 1 certainly encompasses MN-14, and the apoptosis agents listed in Claims 10, 11 and 108, by definition since those claims depend from Claim 1. However, Claim 1 does not cover *any* anti-CEA Mab, *any* apoptosis agent and *any* combination. The only anti-CEA Mabs covered by claim 1 are naked Mabs (ruling out all conjugated Mabs), that are unreactive with human granulocytes (ruling out a class of anti-CEA Mabs that do react with human granulocytes), that have a human IgG1 constant region (ruling out all anti-CEA Mabs with non-human constant regions) and that sensitize CEA-expressing cancers to the subsequent administration of the apoptotic agent. Applicants submit that the scope of Claim 1 covers only a limited sub-group of anti-CEA Mabs that exhibit the properties recited in Claim 1.

Applicants further submit that the Specification in light of general knowledge in the art explicitly discloses how to determine whether or not a given anti-CEA Mab exhibits the recited characteristics and therefore the scope of claim 1 is fully enabled.

A number of antibodies that are unreactive to human granulocytes were known in the art as of the priority date of this application. These include antibodies CE25, T84.66, II-10, II-7, BU-101 and 26/3/13. [See U.S. patent 5,843,708; Cancer Res. 1990 Apr 1;50(7):2128-34; Cancer Res. 1992 Apr 15;52(8):2329-39. Abstracts attached.] The use of an extremely large number of apoptotic agents for treatment of cancer was also very well known in the art as of the instant priority date. In the instant application, Paragraphs [0095]-[0102] describe the claimed composition comprising antibodies that are unreactive with granulocytes; paragraphs [0113]-[0116] teach various therapeutic agents, including apoptotic agents, to be used in the composition; paragraphs [0103]-[0112] teach the methods of treating cancers using such compositions; Example 6 teaches how to determine specificity of therapy, effectiveness of dose and timing and Examples 7-18 illustrate the therapeutic effect of the claimed composition and explain how to interpret the observations and results obtained with the claimed composition.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." [MPEP 2164.01, citing *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, (Fed. Cir. 1988).] A skilled artisan, reading the disclosure of the instant application in light of the general knowledge in the art would be able to make and use the composition claimed in amended Claim 1. Therefore, Applicants respectfully submit that amended Claim 1 is adequately enabled by the specification and request that this rejection be withdrawn.

Claim Rejections – 35 U.S.C. § 103

Claims 1, 10 and 11 were rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al. (Cancer 94:51-61, 2002) (hereafter "Stein") and Blumenthal et al. (Abstract, Cancer Res. 54:142-151, 1994) (hereafter "Blumenthal"). Claims 1, 6 and 7 were rejected under 35

U.S.C. 103(a) as being unpatentable over Stein and Blumenthal as applied to claim 1, further in view of Hansen (U.S. 5,874,540). Claims 1, 10 and 108 were rejected under 35 U.S.C. 103(a) as being unpatentable over Stein and Blumenthal as applied to claim 1, further in view of Griffiths et al. (U.S. 20040043030) and Mani et al. (Abstract, Oncol. 14:52-58, 2000).

The Action states that "Stein teaches compositions for treating nude mice bearing human thyroid tumor comprising the anti-CEA Mab MN-14 in combination with the apoptosis agents, doxorubicin, DTIC, cyclophosphamide, and vincristine, to produce a synergistic effect "significantly enhanced over that observed with either single modality therapy" . . ." [Action at page 7]. The Action further states that Stein does not teach using the composition on human colon cancer but Blumenthal teaches anti-CEA Mab(MN-14) and 5-FU in treating human colon cancer." [Action at page 8]. The Action further states that "One skilled in the art would have been motivated to have produced and been reasonably assured of success in having produced the instant claimed compositions over Stein and Blumenthal. Each of the references teach the comparison between the HM-14 [sic] Mab and apoptosis agents in treating a human cancer, where each of the references concludes independently, that the HM-14 [sic] Mab is more effective than the conventional apoptosis therapy alone."

Applicants respectfully traverse. The cited references of Stein and Blumenthal do not use a naked humanized MN-14 mAb, but a *radiolabeled* murine MN-14 antibody. Stein uses ^{90}Y MN-14 antibody. [See Stein at least at Background on page 51; Paragraph 2, second column on page 52; Materials and Methods at paragraph 4, second column at page 52; Results at paragraph 4, second column at page 53.] Similarly Blumenthal uses ^{131}I-labeled MN-14. [See Blumenthal Abstract, line 3.]

The observation of a synergistic effect using a *radiolabeled* antibody does NOT suggest that the naked antibody will also show a similar effect, since radiolabeled antibodies act by exposing cells to harmful radiation and naked antibodies which do not contain harmful radiation are less potent and sometimes do not show any cancer-killing activity at all. Note also that the conclusion of Blumenthal pertains specifically to *radio*-antibodies. "These preclinical results suggest an advantage to *radio*antibody therapy over one of the most commonly used forms of chemotherapy to treat colorectal cancer." [Blumenthal abstract, emphasis added). Absent undue experimentation, a skilled artisan could not have concluded that the unlabeled naked antibody would show the same synergistic effect as the radiolabeled antibody.

Therefore, Applicants submit that based on the disclosures of Stein and Blumenthal a skilled artisan would not have the motivation nor a reasonable expectation of success in producing the claimed composition which comprises a naked unlabeled humanized antibody (not a radiolabeled murine antibody).

Furthermore, neither Stein nor Blumenthal disclose the element that "administration of the naked anti-CEA MAb to a cancer expressing CEA sensitizes the cancer to the subsequent administration of a cancer therapeutic agent." On the contrary, Stein discusses, as a possible explanation of the enhanced effect, radiosensitization by the chemotherapeutic drug DTIC, not sensitization by the naked anti-CEA MAb to the administration of the drug. [See Stein at column 1, paragraph 2 on page 60.]

For these reasons, Applicants respectfully submit that claim 1 is not prima facie obvious over Stein and Blumenthal. Also, none of the other cited prior art of Hansen, Mani or Griffiths overcomes the deficiencies of Stein or Blumenthal and the claimed composition looks obvious only in hindsight of the disclosure of the instant application. Since claims 6, 7 and 10 depend from claim 1 and include all limitations of claim 1, applicants submit that these claims are also not obvious over the cited prior art. Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

Double patenting

Claims 1, 6, 7, 10, 11 and 108 were rejected on the ground of non-statutory double patenting as being unpatentable over claims 1, 2 and 10 of Griffiths in view of Stein, Blumenthal and Hansen. The Action states that "Griffiths claims a composition for effecting therapy of a tumor in a patient comprising a therapeutic naked antibody and a second therapeutic agent" such as a drug. [See Action at page 14.]

Claim 1 of Griffiths claims "A composition for effecting therapy of a tumor in a patient, comprising: (A) a therapeutic naked antibody or a first conjugate comprising a targeting moiety and a first therapeutic agent, wherein the targeting moiety selectively binds to (i) a marker substance produced by or associated with the tumor and (ii) a low molecular weight hapten or to a second therapeutic agent; (B) optionally, a clearing agent; and (C) a second therapeutic agent or a second conjugate comprising a low molecular weight hapten to which said first conjugate binds and a second therapeutic agent, wherein the second therapeutic agent is the same as or different from the first therapeutic agent." Claim 2 claims "The composition of claim 1, wherein said first and second therapeutic agents are selected from the group consisting of radionuclides, cytokines, drugs, toxins, and boron addends" and claim 10 claims specific embodiments of the drugs. The Action further states that Griffiths discloses a humanized MN-14 as an antibody in the composition.

Applicants submit that nowhere does Griffiths discloses the elements that the naked anti-CEA MAb is unreactive with human granulocytes, that the administration of the naked anti-CEA MAb to a cancer expressing CEA sensitizes the cancer to the subsequent administration of a cancer therapeutic agent or that the combination of the naked anti-CEA MAb and the apoptosis agent is more effective for treatment of human medullary thyroid carcinoma or human colorectal cancer than either the naked anti-CEA MAb or the apoptosis agent alone or the sum of the effects of the naked anti-CEA MAb and the apoptosis agent administered individually.

On page 15, the Action states that Stein teaches the synergy achieved with the antibody/apoptosis combination. However, for the reasons explained above, Applicants submit that Stein does not teach all the elements of the claimed subject matter. Furthermore, neither Blumenthal nor Hansen teach all elements of the claimed subject matter. Therefore, Applicants submit that that the claimed composition is not prima facie obvious over claims 1, 2 and 10 of Griffiths and disclosures of Stein, Blumenthal and Hansen and request that this rejection be withdrawn.

Conclusion

For the reasons stated above, Applicants submit that the all claims are now in condition for allowance and request withdrawal of the rejections.

Respectfully submitted,

Rita P. San

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Rita P. Sanzgiri
Reg. No. 59,846
Phone: 303-447-7720